REMARKS

Claims 1-4, 9-10, 19, 34, 36, 40 and 47 are present in this application. Claims 21-33, 35 and 45 have been cancelled in previous amendments, while claims 5-8, 11-18, 20, 37-39, 41-44 and 46 have been cancelled in the present amendment. Support for the claim amendments is found throughout the specification, and specifically on page 5 lines 13-24, page 9 line 28 - page 10 line 2, page 10 lines 19-21, page 17 lines 24-32, and the Examples on pages 19-30.

Claims 1-5, 9-10, 19, 34-37, 40 and 46-47 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The office action states that the specification, while providing support for a lysine residue at position 44, does not provide a sufficient description for other charged residues at this position. Although the applicant disagrees with the Examiner's position, in order to advance prosecution, claim 1 has been amended to require a lysine residue at this position. In view of this amendment, the rejection has been overcome and should be withdrawn.

It is noted, however, that the applicant believes the specification fully supports a charged residue at position 44. As set forth previously, claim 1 recites a charged residue which is exactly what the Lys group is. This language also excludes other residues that are not described in the specification, such as non-charged residues that do not perform as noted in the invention. The skilled artisan knows what similar or equivalent groups can be used instead of lysine. Furthermore, it is improper to try to restrict applicant's invention to the most preferred embodiment. Therefore, the disclosure is more than sufficient to support a charged residue at position 44.

The Examiner also maintains that the polypeptide that contains the lysine residue is broad with no definite structure and that, due to the low predictability in the field of immunochemistry, the applicant is not entitled to claim such a polypeptide, absent sufficient support by well-established chemical principles or by a sufficient number of examples. The applicant respectfully disagrees. The concept of the invention is to provide a soluble and stable peptide, comprising a scaffold element representing the VH/VL interface, which comprises a lysine residue at position 44, a Leu residue at position 45, and a Trp residue at position 47. It is this crucial scaffold element provides increased stability to the polypeptide, conferred by the Lys residue at position 44. This concept can be applied to <u>any</u> polypeptide which comprises this

scaffold, so the nature of the polypeptide is not critical. Therefore, the disclosure is sufficient and fully supports the claims, and accordingly the rejection should be withdrawn.

Claims 1-5, 9-10, 19, 34-37, 40 and 46-47 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, claim 1 was rejected because the recitation of "without induced mutations or modifications in the original VH/VL interface framework" is allegedly at odds with the specification, which recites for mutations at the VH/VL interface.

Applicant traverses this rejection. The Examiner refers to page 3 last paragraph to support her position that claim 1 is confusing. This paragraph describes a prior art study, which describes isolation of antigen-binding VH domains from a human-phase displayed VH library. A human VH/VL interface of camelid immunoglobulin heavy chain was mimicked to prevent non-specific binding of the VH through its interface for the light chain variable domain, through three mutations in the VH/VL interface. The study, which described in the background of the invention, is not relevant to and cannot be used to contradict the present invention. In fact, as clearly set forth in the previous amendment, the recitation "without induced mutations or modifications in the original VH/VL interface framework" was added to distinguish the invention from the prior art described on page 3. The Applicant is puzzled as to why the Examiner believes that a prior art study described in the background should provide support for the claims.

The Examiner also maintains that page 5 reveals a different concept than that of claim 1. In fact, contrary to the Examiner's position, page 5 (the summary of the invention) precisely describes the subject matter of claim 1. Claim 1 requires a polypeptide comprising "natural framework scaffold of a monoclonal antibody, without any induced mutations or modifications in the original VH/VL interface framework". Page 5 second paragraph exactly describes this concept: "One aspect of the present invention involves a phage-display library of a single-domain of the variable region of the heavy chain of an antibody molecule (VH). The phase display library according to the present invention is based on a natural framework scaffold of a monoclonal antibody, without any induced mutations or modifications in the original VH/VL interface framework residues..." (emphasis added). It is respectfully submitted that the summary of the invention on page 5 clearly and unambiguously describes the subject matter of

the claims, whereas the background of claim 3 describes an unrelated concept. Thus, the claim language is correct and is not indefinite. Accordingly, the rejection should also be withdrawn.

Claims 1-5, 9-10, 19, 34-37, 40 and 46-47 were rejected under 35 U.S.C. 103(a) as being unpatentable over del Rio et al. EP 712,863 ("del Rio") in view of the de Wildt article. The Examiner acknowledges that del Rio does not disclose a polypeptide having a charged residue at position 44, but alleges that de Wildt discloses that heavy chain with Lys residue has the highest affinity to an antigen so that it would be obvious to place a charged residue at position 44. Further, the Examiner contends that the increased affinity provides motivation to make the substitution, and that the function found by the applicant – i.e., a more stable polypeptide, is merely a hitherto unknown property of a known and obvious polypeptide.

Applicant traverses this rejection, and submits that it would not been obvious to replace the Gly residue with a Lys residue in position 44 of the framework in view of de Wildt. de Wildt discloses that the lysine residue in CDR3 contributes to specific binding – i.e., results in increased affinity. In contrast, the present invention is based on the finding that replacing position 44 of the VH/VL interface framework with a lysine residue results in increased stability. The Examiner contends that "it is well known in the art that increased affinity can be achieved if the compound is stable", so that the increased affinity would provide the motivation to make the substitution. This is simply not true. Affinity and stability are entirely different concepts. The term "stable" is defined on page 10 lines 19-21 as "a compound that is sufficiently robust to survive isolation to a useful degree of purity, and formulation into an efficacious therapeutic agent". The term affinity, on the other hand, represents a completely different characteristic of the molecule. "Affinity" describes the interaction between one molecule (antibody or an antibody fragment) and a different molecule (antigen), while "stability" defines the physical state (such as degradation, oligomerization etc.) of the molecule itself and not in relation to another molecule. While preferred compounds should possess high affinity AND increased stability, a compound can have high affinity and high stability, low affinity and high stability, high affinity and low stability, or low stability and low affinity. According to the present invention, the increased stability is the outcome of the specific scaffold of the framework, which contains a charged residue such as lysine at position 44, while the increased affinity is the outcome of the CDR3 sequence. As a result, all the antibody fragments according to the present invention, which have a charged residue such as lysine at position 44 of the framework, are stable, but only

selected ones, with the specific CDR3 sequence, have high affinity and bind antigens of interest. In fact, out of all of the stable molecules, only a small number of specific high affinity molecules are selected via panning cycles from libraries containing millions of VH domains.

This is further explained and embodied in the specification. Example 5 (pages 24-25) describes the biochemical characterization of the VH single domain molecules and stability measurements. As explained, the stability tests are biophysical tests (such as Mass Spectroscopy and Circular Dichroism, Sedimentation equilibrium experiments), which has nothing to do with affinity measurements. In contrast, as explained, improving the affinity is made through "further randomization of selected residues followed by further selection. More efficient is the direct isolation of high affinity binders from the original repertoire by improvement of the library complexity", and not by improvement of the stability. Affinity measurements are described in examples 4 (pages 23-24) and 6 (pages 27-28) and are based on binding assays and surface plasmon resonance assays which are completely different then stability measurements.

Not only does de Wildt not teach that the substitution of a charged residue such as lysine can contribute to stability, the reference also does not teach or suggest incorporation of a charged residue such as lysine in the VH/VL interface framework. It is this crucial scaffold in the VH/VL interface which provides the unexpected stability to the polypeptides of the invention. de Wildt discloses incorporation of a lysine residue in CDR3, and that this results in increased affinity, but the reference does not teach or remotely suggest incorporation of lysine or other charged residues in the VH/VL framework to increase stability. The incorporation of lysine in CDR3 as per de Wildt may provide a polypeptide having high affinity, but this is completely unrelated to the increased stability conferred by the lysine at position 44 of the VH/VL interface. Simply stated, incorporation of a lysine residue in the VH/VL interface resulting in increased stability as taught by the present invention is a concept that is not mentioned, suggested or even contemplated by de Wildt.

Therefore, the advantage taught by de Wildt for increasing affinity by having Lysine residue within the CDR3 sequence would not provide any motivation to increase stability by replacing position 44 of the VH/VL interface framework with a lysine residue. Thus, the skilled artisan would not be led to substitute the lysine residue into the framework as taught by the present invention, so that this rejection should be withdrawn.

Finally, as noted above, a petition to extend the time for responding, as well as a Notice of Appeal, are enclosed.

In view of the above, the entire application is believed to be in condition for allowance, early notice of which would be appreciated. Should any issues remain, a personal or telephonic interview is respectfully requested to discuss the same in order to expedite the allowance of all the claims in this application.

Respectfully submitted,

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